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Neuromuscular electrical stimulation improves exercise tolerance in patients with advanced heart failure on continuous intravenous inotropic support use—randomized controlled trial

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Abstract

Objective: To evaluate the impact of a short-term neuromuscular electrical stimulation program on exercise tolerance in hospitalized patients with advanced heart failure who have suffered an acute decompensation and are under continuous intravenous inotropic support.

Design: A randomized controlled study.

Subjects: Initially, 195 patients hospitalized for decompensated heart failure were recruited, but 70 were randomized.

Intervention: Patients were randomized into two groups: control group subject to the usual care ($n = 35$); neuromuscular electrical stimulation group ($n = 35$) received daily training sessions to both lower extremities for around two weeks.

Main measures: The baseline 6-minute walk test to determine functional capacity was performed 24 hours after hospital admission, and intravenous inotropic support dose was daily checked in all patients. The outcomes were measured in two weeks or at the discharge if the patients were sent back home earlier than two weeks.

Results: After losses of follow-up, a total of 49 patients were included and considered for final analysis (control group, $n = 25$ and neuromuscular electrical stimulation group, $n = 24$). The neuromuscular electrical

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stimulation group presented with a higher 6-minute walk test distance compared to the control group after the study protocol (293 ± 34.78 m vs. 265.8 ± 48.53 m, $P < 0.001$, respectively). Neuromuscular electrical stimulation group also demonstrated a significantly higher dose reduction of dobutamine compared to control group after the study protocol (2.72 ± 1.72 µg/kg/min vs. 3.86 ± 1.61 µg/kg/min, $P = 0.001$, respectively).

Conclusion: A short-term inpatient neuromuscular electrical stimulation rehabilitation protocol improved exercise tolerance and reduced intravenous inotropic support necessity in patients with advanced heart failure suffering a decompensation episode.

Keywords

Cardiac rehabilitation, functional capacity, neuromuscular stimulation, heart failure

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Introduction

Several studies have demonstrated that neuromuscular electrical stimulation therapy significantly improves exercise tolerance and quality of life in patients with advanced heart failure who cannot engage in conventional exercise training.[1–3] To this point, most of these studies were performed in patients with heart failure in the outpatient setting, for over several weeks to months.[4] Few data are available that assess the effects of neuromuscular electrical stimulation as a short-term inpatient intervention for patients with advanced heart failure admitted for acute decompensation. In addition, there are limited studies assessing the functional capacity of patients with advanced heart failure receiving continuous inotropic infusions.

Therefore, the aim of this study was to evaluate the impact of a short-term neuromuscular electrical stimulation program on exercise tolerance in hospitalized patients with advanced heart failure who have suffered an acute decompensation and are under continuous intravenous inotropic support.

Methods

This randomized controlled study was conducted at the São Paulo Hospital—Cardiology Unit of the Federal University of Sao Paulo, Brazil, between January 2010 to December 2014 and was previously approved by Institutional Ethical Research Committee and registered at ClinicalTrials.gov (NCT02668419). Prior to study inclusion, all patients were informed about the study and a signed consent form was obtained from each subject.

Hospitalized patients with advanced heart failure—stage D (left ventricular ejection fraction <30%) determined by echocardiography performed on the day of hospital admission, at rest, through Simpson's method,[5] New York Heart Association class III–IV, diagnosis and management of heart failure,[6] standard medical therapy[7] and continuous inotropic infusions were included. Exclusion criteria were unstable angina pectoris, acute coronary syndromes in the last six months, atrial and ventricular arrhythmias leading to hemodynamic compromise, diabetes mellitus, peripheral vascular disease and neurological or orthopedic conditions that would limit performance during the functional assessment. Patients with chronic obstructive pulmonary disease confirmed by pulmonary function testing according to American Thoracic Society standards were also excluded.[8] Quality of life was performed on admission using the Minnesota Living with Heart Failure Questionnaire to characterize the sample.[9] All patients underwent standard medical therapy beta-1 selective blockers (angiotensin-converting enzyme inhibitors, aldosterone antagonists and other diuretics) as needed during hospitalization.

Patients hospitalized for decompensated heart failure were prospectively randomized into two

groups 24 hours after hospital admission and clinical stabilization; control group: patients underwent a usual care; the neuromuscular electrical stimulation group: patients received daily neuromuscular electrical stimulation sessions to both lower extremities. Randomization was generated by the software "random.org" and allocation secrecy was kept by numbered, sealed, opaque envelopes. The outcome measures were assessed by the same health professional who was blinded to the patients' group allocation.

Study protocol

Usual care group—each session consisted of breathing exercises and global active exercises of the upper and lower limbs in bed. The treatment was applied twice a day during the hospitalization period. The protocol was interrupted if the patient had signs or symptoms suggestive of poor tolerance to exercise: (1) cyanosis, pallor, dizziness, nausea or pre-syncope; (2) chest pain; (3) bradycardia; (4) a drop in systolic blood pressure >15 mm Hg in comparison to baseline; (5) an excessive rise in systolic blood pressure defined as >200 mm Hg; (6) a rise in diastolic blood pressure during exercise >110 mm Hg; (7) fatigue rated ≥6/10 on the perceived exertion Borg (PEB) scale; and/or (8) electrocardiographic signs of cardiac ischemia or ventricular arrhythmias.

Neuromuscular electrical stimulation group—quadriceps and calf muscles of both legs were simultaneously stimulated using self-adhesive surface rectangular electrodes (90 × 50 mm) (FESMED IV; CARCI, Sao Paulo, Brazil). The electrodes were positioned approximately 5 cm below the inguinal fold line and 5 cm above the upper patella border in order to promote quadriceps stimulation; to stimulate the calf muscles, the electrodes were positioned approximately 5 cm under the popliteal fossa and 5 cm over the Achilles tendon. During all session periods, the patients were maintained in the supine Fowler 45° position. Stimulation parameters were set up as follows: biphasic current of 40 Hz, 400-μs pulse duration, mode "on-time" 10 seconds and "off-time" 20 seconds and maximal amplitude of 60 mA. The stimulation intensity progressively increased according to the patient tolerance until a muscular contraction was observed. The stimulation program was performed during the patient's in-hospital period, which lasted around two weeks, twice a day; the session duration was 60 minutes including 5 minutes for warm up and 5 minutes for recovery. Heart rate, blood pressure, respiratory rate and pulse oximetry were monitored throughout the sessions, in all patients. Patients were instructed to leave bed and rest in a bedside chair at least twice a day outside the sessions associated with the protocol.

Outcome measures. Functional capacity was evaluated using the 6-minute walk test, in accordance with American Thoracic Society criteria.[10] For this analysis, a baseline 6-minute walk test was performed 24 hours after hospital admission and clinical stabilization.

During the test, all patients were taking intravenous inotropic drugs administered by an infusion pump which was carried out by the same blinded evaluator who walked at patient's side. The 6-minute walk test would be discontinued if the patient presented with signs or symptoms suggestive of exercise intolerance as described above. The prediction equation proposed by Iwama et al.[11] was used to predict 6-minute walk test distance for all patients. For all patients, the inotropic intravenous dose was adjusted daily by a single clinician (prescriber) blinded to the group allocation, and weaning from inotropic support was based on the improvement in clinical signs.

The follow-up 6-minute walk test and inotropic intravenous dose were measured in two weeks or at the discharge if the patients were sent back home earlier than two weeks.

Statistical analysis

Based on the results of previous studies,[12] the sample size was calculated for detecting at least a 40m difference in 6-minute walk test distance with a power of 80% and alpha risk of 5% ($P < 0.05$). For this study, the sample size needed to achieve the calculated study power was 24 patients per group. This assumption suggested a sample of 48 patients,

resulting in a sample of 70 patients to cover attrition. Variables were described as mean ± standard deviation. The Student's unpaired *t*-test and Mann–Whitney test were used for comparing as appropriate. For intragroup comparison, the Student's paired *t*-test and Wilcoxon test were used as appropriate. The analysis of categorical data was performed by the Pearson chi-square test. The Pearson correlation coefficient was used to evaluate associations between 6-minute walk test distance and the intravenous inotropic support. Statistical analysis was performed by GraphPad Prism 3.0 software (GraphPad Software Inc., San Diego, CA, USA). For all statistical tests, a P-value < 0.05 defined statistical significance.

Results

During the study period, 195 patients were assessed for eligibility, and from that sample, 70 were randomized and allocated into the two groups; after excluding losses of follow-up, 49 patients completed the study (control group, $n = 25$ and neuromuscular electrical stimulation group, $n = 24$) as shown in Figure 1. A total of 11 patients died during the study period (control group, $n = 6$ and neuromuscular electrical stimulation group, $n = 5$).

The groups were homogeneous and no statistical difference was found with respect to key baseline characteristics as shown in Table 1. The protocols were well tolerated by patients of both groups. No muscle soreness and/or electrode-associated skin alterations were observed. The duration of the treatment was 12.13 days in the control group and 13.15 days in the neuromuscular electrical stimulation group ($P = 0.33$).

Regarding functional capacity, the groups were homogeneous on baseline and a significant improvement in 6-minute walk test distance was seen in both groups post-protocol, compared to the baseline values ($P < 0.05$). However, stimulation group exhibited a significantly higher increase compared to the control group after protocol application ($P < 0.001$) (Table 2).

Concerning intravenous inotropic support, both groups were homogeneous at baseline and attained a reduction in the dobutamine dose post-protocol in relation to baseline ($P < 0.001$). When the groups were compared after protocol application, the neuromuscular electrical stimulation group showed a significantly higher dose reduction of dobutamine compared to the control group ($P = 0.001$) (Table 2). Moreover, there was a significant negative correlation between the 6-minute walk test distance and intravenous inotropic support at protocol completion ($r = -0.7$; $P < 0.001$).

Discussion

Our study showed that a short-term inpatient neuromuscular electrical stimulation protocol was able to improve functional capacity, exercise tolerance and reduce the need for intravenous inotropic support at a faster trajectory in patients with advanced heart failure hospitalized for an acute decompensation. This analysis appears to be a novel addition to the literature and further supports the utility of neuromuscular electrical stimulation in this chronic disease population, particularly in those with an advanced disease phenotype.

Conventional methods of exercise rehabilitation (i.e. aerobic and resistance) in patients with New York Heart Association classes III–IV can be limited by dyspnea, fatigue or exhaustion due to low peripheral oxygen supply.[13] Immobilization has been shown to be a factor that may partly contribute to enhance the skeletal muscle weakness in patients hospitalized with heart failure.[14] The current literature suggest that these heart failure patients with advanced disease severity (i.e. New York Heart Association III–IV) benefit from activities that produce muscle contractions to reduce loss of muscle mass that significantly impacts functional capacity.[1,15,16]

Studies have emphasized the need of new rehabilitation approaches for severely compromised heart failure patients who have suffered an acute decompensation episode.[1,3] In this context, neuromuscular electrical stimulation has been used in several studies with a positive impact on functional capacity and quality of life and is being increasingly recommended as a tool for rehabilitation in patients with advanced heart failure and profound functional deficits.[3,4,13,17,18]

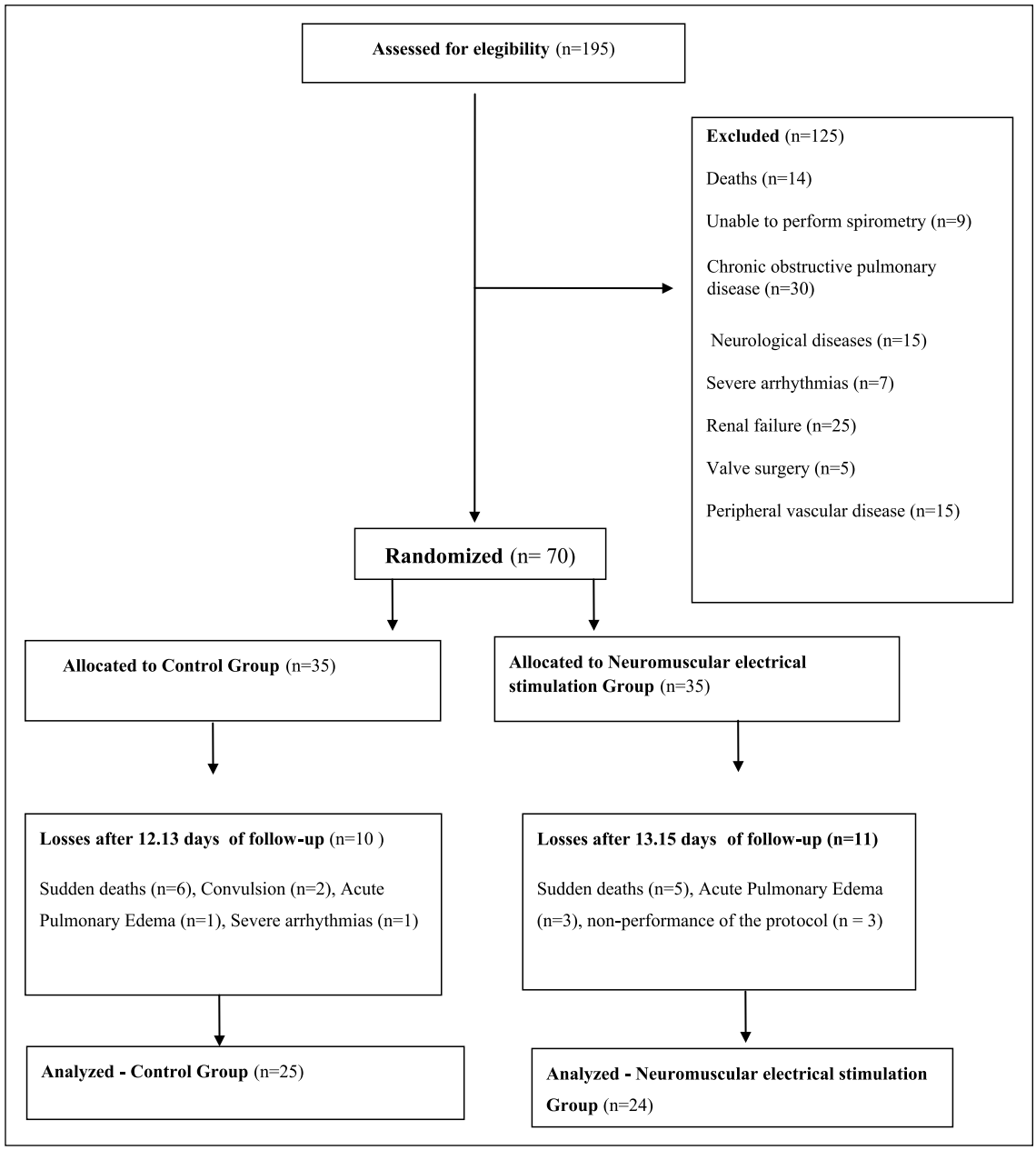

Figure 1. Flowchart of the study.

Nevertheless, most of these studies were conducted in patients with heart failure in the outpatient setting, often for duration of at least eight weeks.[1,4,17] Therefore, a novel aspect of our study was to test the application of neuromuscular electrical stimulation over a short period of time in patients with

Table 1. Demographic and clinical characteristics.

Variables	Control group ($n=25$)	Neuromuscular electrical stimulation group ($n=24$)	*P*-value
Age (years), mean (SD)	51.52 (11.03)	52.58 (14.71)	0.40
Female/Male, *n*	3/22	5/19	0.20
BMI (kg/m^2), mean (SD)	23.61 (4.08)	22.14 (2.47)	0.08
Etiology, *n*	15 ischemic 02 idiopathic 07 hypertensive 01 valve	14 ischemic 04 idiopathic 05 hypertensive 01 non-compact myocardium	0.45
ICD/pacemaker, *n*	13	15	0.22
LVEF, mean (SD)	0.25 (0.03)	0.27 (0.04)	0.09
MLHFQ score, mean (SD)	72.38 (12.11)	77.10 (12.03)	0.10
Pulmonary function			
FVC (L), mean (SD)	2.94 (0.67)	2.84 (0.82)	0.34
% predicted	75.92 (9.08)	74.84 (10.5)	
FEV1 (L), mean (SD)	2.55 (0.61)	2.74 (0.74)	0.25
% predicted	84.41 (12.54)	87.65 (9.58)	
Drug therapy			
Angiotensin converting enzyme inhibitors (mg/day), mean (SD)	20.22 (16.74)	22.30 (21.31)	0.35
Furosemide (mg/day), mean (SD)	30.45 (10.24)	29.20 (10.21)	0.32
Length of exercise sessions (days), mean (SD)	12.13 (1.21)	13.15 (2.4)	0.33

SD: standard deviation of the mean; BMI: body mass index; FVC: forced vital capacity; FEV1: forced expiratory volume in 1 second; ICD: implanted cardioverter defibrillator; LVEF: left ventricular ejection fraction; MLHFQ: Minnesota Living with Heart Failure Questionnaire.

Table 2. Distance in the 6-minute walk test and intravenous inotropic support between groups after study protocol.

Variables	Control group ($n=25$)		Neuromuscular electrical stimulation group ($n=24$)	
	Baseline	Post-protocol	Baseline	Post-protocol
Distance (m), mean (SD)	237.8 (40.50)	265.8 (48.53)*	238 (47.43)	293 (34.78)*†
% predicted	40.05 (6.37)		42.52 (9.57)	
Dobutamine (μg/kg/min), mean (SD)	8.02 (3.81)	3.86 (1.61)*	8.87 (3.63)	2.72 (1.72)*†

SD: standard deviation of the mean.
*$P<0.05$ baseline vs. post-protocol; †$P<0.05$ control group vs. neuromuscular electrical stimulation group study post-protocol.

advanced heart failure suffering an acute decompensation and requiring continuous dobutamine in the inpatient setting.

Previous studies have shown that heart failure patients with a phenotype similar to those included in the current analysis have a higher risk of morbidity (high risk of re-hospitalization) and mortality.[19,20] In our study, both groups presented at baseline with a mean 6-minute walk test distance less than 300 m, highlighting the advanced disease

severity and clinical fragility of these patients. Even so, there were no adverse events with the use of neuromuscular electrical stimulation, indicating the safety of this therapeutic intervention in compromised patients, even in patients with implanted cardioverter defibrillators, consistent with previous studies.[17,21]

With respect to improvements in functional capacity, both groups demonstrated a significant increase in 6-minute walk test distance after the exercise protocol. However, the patients in the neuromuscular electrical stimulation arm demonstrated an increase of 56 m in relation to baseline values, while the usual care group achieved an increase of 28 m. These findings support the ability of neuromuscular electrical stimulation to significantly augment functional recovery during inpatient care in patients with advanced heart failure. Previous investigations have stated an increase in 6-minute walk test of at least 45 m is needed to support therapeutic efficacy.[22] However, previous work has not assessed the 6-minute walk test distance improvement indicative of a meaningful clinical difference in heart failure patients undergoing continuous inotropic infusion. Even so, the results of this study are consistent with the previously defined criteria for a meaningful clinical improvement by 6-minute walk test distance criteria in patients receiving neuromuscular electrical stimulation. Our results are consistent with a recent study[23] where hospitalized patients with heart failure (New York Heart Association II–III) without inotropic support underwent daily neuromuscular electrical stimulation sessions for 15 days and also presented with a clinically significant increase in 6-minute walk test distance.

Studies showing that patients who covered a longer 6-minute walk test distance have a decreased likelihood of death or hospitalization for inotropic or mechanical support.[19,20,24] In this context, our findings suggest that neuromuscular electrical stimulation may improve outcome by achieving a significantly greater 6-minute walk test distance; future research is needed to address this question. Despite widespread use, evidences indicate that dobutamine is not associated with mortality reduction and is in fact associated with an increase in mortality. It was suggested that more research is needed to define the clinical role of dobutamine in the treatment of advanced heart failure.[25] Our findings indicate that neuromuscular electrical stimulation may accelerate dobutamine weaning which has clear benefits.

When the correlation among the functional capacity and the intravenous inotropic support in all patients was performed after protocol completion, we found a reduced need of inotropic support in patients with a longer 6-minute walk test distance; neuromuscular electrical stimulation appears to significantly improve the distance achieved.

We believe that the mechanism for a positive impact on functional status and the reduced need for dobutamine observed in the neuromuscular electrical stimulation group has a physiologic rationale similar to traditional exercise training studies in patients with heart failure.[2,5] The positive impact of neuromuscular electrical stimulation has been attributed to several factors such as increased aerobic enzyme activity due to an augment of peripheral blood flow, enhanced muscle vascularization and mitochondrial volume and inhibition of protein degradation.[26] The potential ability of neuromuscular electrical stimulation to improve the peripheral vasodilator response, with a reduction in peripheral vascular resistance and a concomitant decrease in cardiac afterload that reduces end-systolic wall stress and consequently decreases inotropic overload,[2,13,27] is a particularly attractive physiologic mechanism of improvement for patients with advanced heart failure. Besides, studies indicate that exercise training to be an important factor to regulation of cardiac adrenergic beta receptors that are deficient in patients with heart failure, and this fact appears to contribute to weaning from dobutamine.[28]

This study has limitations. First, the results are limited by a lack of a sham neuromuscular electrical stimulation arm in patients assigned to the control group. Second, a cut-off that determines the prognostic value and clinical impact of an increase in the distance covered during inpatient rehabilitation in patients with advanced heart failure under continuous use of dobutamine has not yet been reported, limiting conclusions that can be drawn

from our findings. Third, the patients lost for follow-up, who had complications like convulsion, acute pulmonary edema and severe arrhythmias, had no final outcome evaluation. Fourth, in this study, we looked only at the immediate effects, and the long-term benefits still need a further study. Thus, additional research is needed in this area.

In conclusion, a short-term inpatient neuromuscular electrical stimulation rehabilitation protocol improved exercise tolerance and reduced continuous intravenous inotropic support necessity in patients with advanced heart failure suffering a decompensation episode. As such, if confirmed by additional studies, the use of neuromuscular electrical stimulation in this setting may become a standard of care.

Clinical Messages

- Our results suggest that in patients admitted to hospital with decompensated advanced heart failure, neuromuscular electrical stimulation may improve exercise tolerance and reduce the need for inotropic support.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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